Expanded Topic Brief: Cancer Survivorship in Young Adults

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Purpose: This document summarizes the information addressing a nomination submitted on May 3, 2021 through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue: While guidelines exist for survivors of childhood and adult cancers, there is a lack of guidelines specifically for survivors of young adult cancers. Despite the different needs of this group, guidance is often extrapolated from other age groups.

Program Decision and Key Findings:

- We found a group of studies with varied cancer types, treatment types, and outcome measures examining post-acute adverse events of treatment in young adult cancer survivors (key question 1 (KQ1)). We did not find any studies for KQ2 on the effectiveness and harms of monitoring/surveillance or screening for secondary cancers and late effects of cancer treatment in young adult cancer survivors. Due to the heterogeneity of the studies for KQ1, a systematic review will not be developed.

- Instead, we present in this expanded topic brief the summary findings from 37 studies we identified for KQ1. Tables 2a-f are organized by outcome categories and may serve as a reference for those interested in a map of recent studies on the topic.

Background

Each year, about five percent (89,000) of cancer diagnoses in the United States are in young people between the ages of 15 and 39.[1] From 2008 to 2010, the annual cost for cancer survivors ages 18 to 64 was $16,213 per survivor.[2] While little evaluation of the financial impact on young adults and their families has been conducted, this population is particularly vulnerable to the financial burden of cancer care.[3]

The needs of young adult cancer survivors may include addressing anxiety about cancer recurrence, fatigue, depression,[4] fertility issues,[5] and obtaining assistance to address their health and supportive care needs.[4] Harms due to treatment may also include premature or accelerated aging due to chemotherapy, and radiation-induced second cancers and cardiovascular disease.[6]

Currently, guidelines exist for survivors of childhood and adult cancers, but not specifically for survivors of young adult cancers. Despite differences in needs for this group, guidance is often extrapolated from other age groups.

Nomination Summary

The American Society of Clinical Oncology (ASCO) originally requested a systematic review to inform the development of clinical practice guidelines for the care of young adult cancer survivors. The cancer and treatment types, and outcome measures in the studies identified were too varied to synthesize in a systematic review. The nominators felt that, considering the nature of the evidence base, an expanded topic brief would be useful to provide a map of the recent studies that have been published. Consequently, we included Tables 2a-f which outline the 37 studies addressing KQ1.

Scope

1. What are the post-acute adverse effects of cancer treatment in cancer survivors diagnosed as young adults?
    a. What are the relative poste-acute adverse effects associated with different cancer treatments or features of treatment (e.g., different dosages) in cancer survivors diagnosed as young adults?
2. What is the effectiveness and harms of monitoring/surveillance or screening for secondary cancers and late effects of cancer treatment in cancer survivors diagnosed as young adults?

Table 1. Questions and PICOT (population, intervention, comparator, outcome, and timing)

Questions	1. Post-acute adverse events of treatment in young adult cancer survivors	2. Effectiveness and harms of monitoring/surveillance in young adult cancer survivors
Population	Cancer survivors (history of any cancer diagnosis; no longer actively receiving cancer therapy) who were diagnosed as young adults (18-39 years old)	Cancer survivors (history of any cancer diagnosis; no longer actively receiving cancer therapy) who were diagnosed as young adults (18-39 years old)
Interventions	Any treatment for cancer (e.g., surgery, chemotherapy, radiation, immunotherapy, transplantation, combinations of therapies)	Any monitoring/surveillance or screening (e.g., ultrasound, echocardiogram, colonoscopy, mammography) for secondary cancers and other late effects as a consequence of cancer treatment
Comparators	Other cancer treatment; no comparator For KQ1a: Other cancer treatments; other treatment features (e.g., different dosages)	No monitoring/surveillance, or different (e.g., less frequent, less invasive) monitoring/surveillance interval or type
Outcomes	Long-term effects of treatment: Cause-specific mortality (from other cause-secondary cancer, any treatment-related cause); Incidence of non-primary cancers;	Incidence of morbidity and cause-specific mortality (secondary cancer and late effects as a consequence of, cancer treatment); Incidence of secondary cancer; Harms of monitoring/surveillance: false positive findings, anxiety, false positive biopsies, false negative findings, false

	Chronic conditions (e.g., cardiovascular disease, hypertension, infertility, diabetes, musculoskeletal bone conditions); Psychosocial issues (e.g., social withdrawal, relationship problems, dependent living, body image, sexual health); Neurocognitive issues (e.g., learning deficits, functional deficits, behavioral changes, diminished IQ)	reassurance, overdiagnosis and resulting overtreatment, and radiation exposure
Timing	Minimum study follow-up time of 1 year	Minimum study follow-up time of 1 year

Abbreviations: IQ=intelligence quotient; KQ=key question.

Assessment Methods

See Appendix A.

Summary of Literature Findings

We did not find systematic reviews for KQ1, and found 37 studies of varying cancer diagnoses, treatment types, and outcome measures addressing KQ1. Tables 2a-f below provide summaries of the studies of varying cancer type, treatment type, and outcome measures, categorized by outcomes reported. These tables may serve as a reference map of studies addressing KQ1.
We found no systematic reviews or primary studies addressing KQ2.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

Table 2a. Outcome Category: General Late Effects

Author, Year	Cancer Type	Treatment Type	Study Type	Outcomes	Timing of outcome measurements	Key Findings
Lim, 2020[7]	Brain/skull base tumors	Pencil beam scanning proton therapy	Prospective	Late toxicity	≥1 year follow-up; median 5.5 years post-diagnosis	Local only and distant only (CNS) failures were observed at 13.6% and 0.6%, respectively. Crude late toxicity rates by grade (G) were 26.2% G1, 37.8% G2, 12.2% G3, 0.6% G4 (retinopathy), and 0.6% G5 (brainstem hemorrhage). The 6-year cumulative incidences for any late PT-related pituitary, ototoxicity, and neurotoxicity were 36.3%, 18.3%, and 25.6%; the high-grade (≥G3) ototoxicity and neurotoxicity were 3.4% and 2.9%, respectively. No secondary malignancies were observed.
Abrahao, 2020[8]	Non-Hodgkin lymphoma	Any	Retrospective	Late effects	10 years post-diagnosis	Highest incident diseases were endocrine (18.5%), cardiovascular (11.7%), respiratory (5.0%), SPM (2.6%), renal and neurologic (2.2%), liver/pancreatic (2.0%), and avascular necrosis (1.2%). Incidence for all late effects was higher among HIV-infected survivors, especially for SPM. Among HIV-uninfected patients, public or no health insurance and haematopoietic stem cell transplant were associated with greater risk of most late effects.
Abrahao, 2020[9]	Acute myeloid leukemia	Any	Retrospective	Late effects	10 years post-diagnosis	The most common late effects were endocrine (26.1%), cardiovascular (18.6%) and respiratory (6.6%), followed by neurologic (4.9%), liver/pancreatic (4.3%), renal (3.1%), avascular necrosis (2.7%) and SPM (2.4%). The cumulative incidence of late effects was higher in those who were receiving haematopoietic stem cell transplant, except for those with SPM; incidences were higher among those with avascular necrosis. AYAs of Hispanic, Black or Asian/Pacific Islander (vs non-Hispanic White) race/ethnicity and those who resided in lower socio-economic neighborhoods were at higher risk of numerous late effects.

Author, Year	Cancer Type	Treatment Type	Study Type	Outcomes	Timing of outcome measurements	Key Findings
Chao, 2016[10]	Any	Any	Retrospective	CAD, heart failure, stroke	2 years post-treatment	Survivors had more than twice the risk of developing CVD than patients without cancer, with survivors of leukemia and breast cancer at the highest risk. Cardiovascular risk factors (i.e., diabetes, hypertension, and dyslipidemia) increased risk of CVD. Those who developed CVD had an 11-fold increase in overall mortality risk compared to survivors without CVD.
Chao, 2020[11]	Any	Radiation therapy, chemotherapy	Retrospective	Chronic comorbidities	12 years post-treatment	The incidence of nearly all comorbidities examined was significantly greater in AYA survivors of cancer than people without cancer and 40% had multiple comorbidities. Radiation was associated with hearing loss, vision loss, stroke, thyroid disorders, cardiomyopathy or heart failure, and diabetes. Chemotherapy was associated with cardiomyopathy or heart failure, premature ovarian failure, avascular necrosis, pulmonary fibrosis, and osteoporosis.
Hamilton, 2019[12]	Head and neck	Radiation therapy	Retrospective	Late toxicities	≥5 years post-diagnosis	Most (78%) patients developed late effects, the most common of which were xerostomia (44%), skin changes (28%), neck fibrosis (22%), nasal crusting (16%), epistaxis (16%), and dental decay (14%).
Liuhto, 2020[13]	Any	Any	Retrospective	Morbidity due to renal and bone metabolism diseases	5 years post-treatment	Elevated hazard ratios for scoliosis, osteoporosis, osteonecrosis, nephritis, and kidney failure. For those with a renal outcome, there was increased risk of developing bone metabolism disease outcomes.
Rugbjerg, 2016[14]	Any	NR	Retrospective	Hospitalizations	Median 14 years post-diagnosis	Cancer survivors had 1.38 times the risk of hospitalizations than population controls. The highest risk of hospitalizations was for diseases of blood and blood-forming organs, infectious and parasitic diseases, and malignant neoplasms. Survivors of leukemia, brain cancer, and Hodgkin lymphoma were at greatest risk for hospitalization.

Author, Year	Cancer Type	Treatment Type	Study Type	Outcomes	Timing of outcome measurements	Key Findings
Semrad, 2021[15]	Differentiated thyroid cancer	Any	Retrospective	Secondary medical conditions	10 years post-diagnosis	Male survivors had higher incidence of diabetes mellitus and CVD, but lower asthma and hematologic disorders. The cumulative incidence of subsequent cancers, diabetes mellitus, leukocytosis, and cardiovascular diagnoses increased with age at diagnosis. For disorders related to diagnosis and treatment of differentiated thyroid cancer (disorders of calcium and phosphorus metabolism, hypertension, and other diseases of the heart), the incidence rose continuously from 2 to 10 years post-diagnosis, but rates varied based on age and sex.
Bohn, 2019[16]	Breast cancer stages I-III, colorectal cancer, acute lymphoblastic leukemia, non-Hodgkin lymphoma, malignant melanoma	Any	Cross-sectional	Chronic fatigue	≥5 years post-diagnosis	Twenty-five percent of survivors reported CF. More survivors of breast cancer (29%), colorectal cancer (29%), and non-Hodgkin lymphoma (27%) reported CF than survivors of malignant melanoma (15%). CF was associated with systemic treatment combined with surgery and/or radiotherapy, comorbidity, pain, numbness in hands/feet, ad depressive symptoms.
Feldman, 2018[17]	Testicular cancer	Cisplatin-based chemotherapy	Cross-sectional	Measures of CVD	>1 year post-treatment	Survivors had higher systolic blood pressure than controls, despite that fewer were smokers. Mean Framingham Risk Score evaluating risk of CVD did not differ between survivors and controls.

Abbreviations: AYA=adolescents and young adults; CAD=coronary artery disease; CF=chronic fatigue; CNS=central nervous system; CVD=cardiovascular disease; HIV=human immunodeficiency virus; NR=not reported; PT=proton therapy; SPM=second primary malignancies.

Table 2b. Outcome Category: Secondary Cancer

Author, Year	Cancer Type	Treatment Type	Study Type	Outcomes	Timing of outcome measurements	Key Findings
Chao, 2019[18]	Any	Radiation therapy, chemotherapy	Retrospective	Incidence, risk factors, and mortality for SMN	Measured over 20 years	Risk of SMN is increased in AYA cancer survivors and factors such as older age, female sex, white race, and use of radiotherapy was associated with increased risk, but no such association was found with use of chemotherapy.
Lee, 2016[19]	Any	Any	Retrospective	SMN: standardized incidence ratio, absolute excess risk, cumulative incidence	≥5 years post-diagnosis	Five percent (7384/148,558) of survivors developed an SMN five years after the original diagnosis. The cumulative incidence of SMN at 30 years was 13.9%, most commonly breast cancer, gastrointestinal cancer, genital cancers, and melanoma. Those who had received radiation therapy had a higher cumulative incidence of SMN.
Lo, 2021[20]	Lymphoma	Radiation therapy	Retrospective	Secondary malignancy, late effects	≥5 years post-treatment (median 19.1 years for secondary malignancy, 7.2 years for other outcomes)	The most prevalent late effect was hypothyroidism. The CI of in-field secondary malignancy was 0.4 ± 0.4% at 10 years and 2.8 ± 1.2% at 20 years. CI of symptomatic pulmonary toxicity was 4.6 ± 1.5% and 6.8 ± 2.0% at 5 and 10 years, respectively, and was higher in patients receiving multiple RT courses (p = 0.009). Esophageal complications occurred at a CI of 1.4 ± 0.8% at 5 years and 2.2 ± 1.1% at 10 years. CI of xerostomia/dental decay was 2.6 ± 1.3% at 5 years and 4.9 ± 2.1% at 10 years. CI of cardiac disease was at 2.3 ± 0.9% at 5 years and 4.4 ± 1.5% at 10 years. CI of infertility was 6.5 ± 1.6% at 5 years and 9.4 ± 2.1% at 10 years.
Muffly, 2020[21]	Acute lymphoblastic leukemia	Any	Retrospective	Secondary neoplasms, late effects	10 years post-diagnosis	Estimated 10-year CI of late effects: endocrine (28.7%), cardiac (17.0%), avascular necrosis (9.6%), liver (6.5%), respiratory (6.2%), seizure and/or stroke (4.3%), renal (3.1%), and secondary neoplasms (1.4%). Public or no

Author, Year	Cancer Type	Treatment Type	Study Type	Outcomes	Timing of outcome measurements	Key Findings
						insurance and receipt of hematopoietic cell transplantation were associated with all measured late effects.
Xie, 2018[22]	Breast cancer	Surgery +/- radiotherapy	Retrospective	Secondary malignancy, malignancy-free survival	≥1 year(s) post-treatment (median 11.8 years)	Second malignancies were detected in 1495 (6.6%) of survivors (3.7% contralateral breast cancer, 2.9% non- breast second malignancies, and 0.7% high-dose site second malignancies). Five-, 10-, 15-, and 20-year all second malignancy-free survivals in RT and non-RT groups were 89.5% versus 85.4%, 80.1% versus 75.0%, 72.9% versus 67.9%, and 65.6% versus 61.8% (P<.0001).

Abbreviations*:* AYA=adolescents and young adults*;* CI=cumulative incidence*;* RT=radiation therapy*;* SMN=secondary malignant neoplasms.

Table 2c. Outcome Category: Mortality

Author, Year	Cancer Type	Treatment Type	Study Type	Outcomes	Timing of outcome measurements	Key Findings
Armenian, 2020[23]	Any	Radiation therapy, chemotherapy	Retrospective	Mortality rates	Measured at over 20 years	The risk of death in AYA cancer survivors was about 10 times higher than noncancer counterparts. Radiation exposure was associated with a 50% increase in risk of mortality from secondary malignancies, but this risk was not found with chemotherapy agents (alkylating agents, anthracyclines, platinum agents, or epipodophyllotoxins).
Bhuller, 2016[24]	Hodgkin lymphoma	Any	Retrospective	Mortality, late effects	≥5 years post-diagnosis	Sixty (13.6%) survivors had late mortality with excess deaths from secondary cancers and non-malignant disease. Excess secondary cancers were associated with radiotherapy and female gender. Hospitalization increased with combined modality therapy, chemotherapy alone, and recent treatment era.
Goldfarb, 2018[25]	Acute leukemia, lymphoma, sarcoma, colorectal cancer, female breast cancer, central nervous system cancer, melanoma, cervical cancer, thyroid cancer, germ cell cancer	NR	Retrospective	Mortality, second primary malignancy	≥5 years post-diagnosis (median 11.4 years)	Most survivors who developed a SPM were diagnosed with the primary malignancy between ages 26 and 39 (74.2%), and the SPM diagnosed within 1 to 5 years (72.9%) of the primary diagnosis. Those who developed a SPM 1-5 years after primary diagnosis had an increased risk of death from cancer or any cause, compared to a later (≥6 years) diagnosis of second malignancy, specifically for secondary malignancies that were leukemia, colorectal, breast, or central nervous system cancers.
Suh, 2020[26]	leukemia, central	Any	Retrospective	Mortality, late effects	Median 21 years post-diagnosis	Standardized mortality rate compared to the general population for all-cause mortality was 5.9

Author, Year	Cancer Type	Treatment Type	Study Type	Outcomes	Timing of outcome measurements	Key Findings
	nervous system malignancy, Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms tumor, neuroblastoma, soft-tissue sarcoma, bone cancer					(95% CI, 5.5-6.2). AYA survivors had lower standardized mortality rates for death from late effects than childhood cancer survivors, and both groups were at greater risk of severe/disabling, life-threatening, or fatal late effects compared to same age siblings, though the hazard ratio for AYA survivors was lower, as were hazard ratios for grade 3-5 cardiac, endocrine, and musculoskeletal conditions.
Tzikas, 2020[27]	triple-negative breast cancer	Any	Retrospective	Survival	Median 4.5 years post-diagnosis	Older survivors had shorter survival times, recurrence-free survival, distant disease-free survival, and breast cancer-specific survival than young adults, but not after adjusting for adjuvant/neoadjuvant chemotherapy.

Abbreviations: AYA= adolescents and young adults; NR=not reported; SPM=second primary malignancy

Table 2d. Outcome Category: Psychological/Social Effects

Author, Year	Cancer Type	Treatment Type	Study Type	Outcomes	Timing of outcome measurements	Key Findings
Wettergren, 2017[28]	Any	Surgery, radiation, chemotherapy	Prospective	Sexual function and intimate relationships	Measured at 1 and 2 years post-cancer diagnosis	Approximately half of AYA cancer survivors surveyed reported negative effects on sexual function at 1 year post-diagnosis, and 70% of those reported continued negative perceptions a year later.
Ahomaki, 2019[29]	Any	NR	Retrospective	First time antidepressant medication purchases	NR	Hazard ratios for first time antidepressant medication purchases were increased in survivors compared to siblings.
Olsson, 2018[30]	Any	Any	Cross-sectional	Questionnaire addressing psychosocial health, body image and sexuality, fertility, education, work, leisure	Median 4 years post-diagnosis	Both male and female survivors had higher relative risk of feeling less attractive due to scars, compared to controls, and feeling of attractiveness was negatively related to the size of scars in both cancer and control groups. Age (25-30 yrs vs $\geq$ 31 yrs), lower education, frequent exercise, and self-reported presence of depression were associated with feelings of low attractiveness due to scars.
Shay, 2016[31]	Any, majority lymphoma or testicular cancer	Chemotherapy, radiation, surgery	Cross-sectional	Fear of cancer recurrence	< 5 years out from treatment	Prevalence of fear of recurrence of cancer was higher in AYA survivors (85.2%) than older adults (79.7%). In AYA survivors, being employed and less than five years off treatment were positively associated with fear of recurrence, and those with thyroid cancer and those who participated in a clinical trial were less likely to experience fear of recurrence.

Abbreviations: AYA= adolescents and young adults; NR=not reported

Table 2e. Outcome Category: Reproductive Effects

Author, Year	Cancer Type	Treatment Type	Study Type	Outcomes	Timing of outcome measurements	Key Findings
Chemerinski, 2020[32]	Any	Chemotherapy	Prospective	Symptoms of menopause, early follicular phase hormones, ultrasound examinations	≥1 year post-treatment; average 3 years of follow-up	More survivors than similar-aged controls reported vasomotor symptoms, similarly to late reproductive-aged controls. Survivors had more vaginal dryness than both control groups. FSH levels were higher in those with than without vasomotor symptoms.
Johnson, 2016[33]	Any	Alkylating agent chemotherapy	Prospective	Integrated urinary pregnanediol glucuronide and estrone conjugates, urinary excretion of gonadotropins (FSH and LH)	≥1 year post-treatment	Cycle length, luteal phase length, and evidence of luteal activity were similar between groups. Ovarian reserve was impaired in survivors compared to same-age controls, but similar to late reproductive age controls. Peak PDG levels were similar in survivors and same-age controls, and higher than in late reproductive age controls. Survivors had higher E1c levels than both control groups. Urinary gonadotropins did not vary among groups.
Su, 2020[34]	Any	Radiation, surgery, chemotherapy, biologic therapy, bone marrow or stem cell transplant, endocrine therapy	Prospective	Trajectory of ovarian function, anti-Mullerian hormone levels	Dried blood spots collected every 6 months for up to 18 months, and the AMH trajectory was modeled	The trajectory of projected AMH levels varied based on degree of treatment gonadotoxicity. Younger age was overall associated with better trajectories but was not protective with highly gonadotoxic treatments.
Abe, 2016[35]	Any	Chemotherapy	Retrospective	Resumption of menstruation, whether the patient gave birth after treatment	NR	Fifty-one percent (57/112) of the women survivors had iatrogenic amenorrhea.
Chin, 2016[36]	Any	Any	Retrospective	Reduced fertility (failure to achieve desired family size, childlessness, and not	≥2 years post-diagnosis	Women with hypothyroidism after cancer treatment were twice as likely to fail to achieve their desired family size, and be childless, and were more likely to have

Author, Year	Cancer Type	Treatment Type	Study Type	Outcomes	Timing of outcome measurements	Key Findings
				achieving pregnancy after at least 6 months of regular unprotected intercourse)		unprotected intercourse for at least 6 months without conceiving.
Benedict, 2018[37]	Any	Gonadotoxic treatment (i.e., systemic chemotherapy, pelvic radiotherapy, and/or pelvic surgery affecting reproductive function)	Cross-sectional	Quality of life	≥1 year post-treatment	Lower QOL was associated with being unemployed and having lower household income. Survivors struggled most with feelings of lack of control over their lives, but ratings of general QOL, happiness, and life satisfaction were higher. QOL did not vary by fertility status, history of fertility preservation, or desire for future children.
Hartnett, 2018[38]	Any	Chemotherapy with and without radiation	Cross-sectional	Preterm birth, birthweight/birthweight for gestational age, Cesarean section	≤1 year to >5 years post-diagnosis	Women who conceived ≤1 year after starting chemotherapy had higher risks of preterm birth than control women, while women who conceived ≥1 year after starting chemotherapy without radiation or ≥2 years after chemotherapy with radiation did not. In breast cancer survivors, those who conceived >1 year after starting chemotherapy without radiation or ≥2 years after chemotherapy with radiation did not have a higher risk of preterm birth. In cervical cancer survivors, the risk was somewhat lower in pregnancies conceived after the first year.
Jacobson, 2016[39]	Any	Any	Cross-sectional	Amenorrhea (≥6 months without menses) and resumption of menses	≥2 years post-diagnosis	Amenorrhea occurred in 31.6% of survivors. In women treated with chemotherapy, older age at diagnosis (30-35 years) and nulligravidity were risk factors for amenorrhea. In survivors with amenorrhea, menses resumed for most (70%) within 2 years of treatment for 90% of survivors. Breast cancer survivors had a greater delay (> 1 year) of resumption of menses

Author, Year	Cancer Type	Treatment Type	Study Type	Outcomes	Timing of outcome measurements	Key Findings
						compared with lymphoma and pelvic-area cancer survivors. Older age, chemotherapy, and radiation were associated with longer time to return to menses, and older women were more likely to have irregular cycles when menses returned.
Shandley, 2017[40]	Breast cancer	Tamoxifen	Cross-sectional	Time to first child after cancer diagnosis, clinical measures of ovarian reserve (AMH and AFC)	≥2 years post-diagnosis	Survivors who used tamoxifen were less likely to have a child (HR=0.25). Survivors who used tamoxifen had a mean AMH level 2.47 times higher than survivors who had not used tamoxifen. AFC was also higher in the tamoxifen group.
Shandley, 2018[41]	Any	Any	Cross-sectional	Infertility, time to first pregnancy after diagnosis, measures of ovarian reserve (AMH, AFC)	≥2 years post-diagnosis	Polycystic ovarian syndrome was reported in 7.2% of survivors, with 52.5% receiving gonadotoxic treatment. Survivors with PCOS, both exposed and unexposed to gonadotoxic treatment, were more likely to experience infertility than unexposed survivors without PCOS and were more likely to have fewer children than desired. Survivors without PCOS and treated with gonadotoxic agents had the lowest levels of ovarian reserves and control women with PCOS had the highest.

Abbreviations: AFC=antral follicle count; AMH=anti-Mullerian hormone; AYA= adolescents and young adults; FSH= follicular stimulating hormone; HR=hazard ratio; LH=leutenizing hormone; PCOS=polycystic ovarian syndrome; PDG=pregnanediol; QOL=quality of life.

Table 2f. Outcome Category: Bone Mineral Density Effects

Author, Year	Cancer Type	Treatment Type	Study Type	Outcomes	Timing of outcome measurements	Key Findings
Isaksson, 2017[42]	Testicular germ cell	Surveillance, 1-2 cycles of chemotherapy, 3-4 cycles of chemotherapy, >4 cycles of chemotherapy, radiation therapy	Prospective	Bone mineral density, testosterone, luteinizing hormone	7-10 years of follow-up	Cancer treatment was not associated with BMD, but hypogonadism was associated with decreased BMD.
Ha, 2020[43]	Hematologic malignancies	Allogeneic hematopoietic stem cell transplantation (followed by hormone replacement therapy)	Retrospective	Bone mineral density	3 years of follow-up	Patients who received hormone replacement therapy following hematopoietic stem cell transplantation had increased BMD compared to no hormone replacement therapy.

Abbreviations: BMD=bone mineral density.

Summary of Selection Criteria Assessment

While guidelines for cancer survivors who were diagnosed as children or adults exist, the needs of cancer survivors who were diagnosed as young adults differ from those of other age groups and guidelines are lacking. The nominators requested a systematic review to use in the development of a guideline for this age group of cancer survivors. While the body of literature does not lend itself to a synthesis in a systematic review at this time due to varied cancer types, treatment types, and outcome measures, we present the studies that match KQ1 in Tables 2a-f as a map of this diverse body of primary studies. We did not find any evidence to address the effectiveness and harms of surveillance or screening in this population (KQ2).

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

References

1. NIH. Adolescents and Young Adults with Cancer. doi: https://www.cancer.gov/types/aya.
2. Guy GP, Jr., Ekwueme DU, Yabroff KR, et al. Economic burden of cancer survivorship among adults in the United States. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(30):3749-57. doi: https://doi.org/10.1200/JCO.2013.49.1241. PMID: 24043731.
3. Salsman JM, Danhauer SC, Moore JB, et al. Systematic review of financial burden assessment in cancer: Evaluation of measures and utility among adolescents and young adults and caregivers. Cancer. 2021 Jun 1;127(11):1739-48. doi: https://doi.org/10.1002/cncr.33559. PMID: 33849081.
4. Jones JM, Fitch M, Bongard J, et al. The Needs and Experiences of Post-Treatment Adolescent and Young Adult Cancer Survivors. Journal of clinical medicine. 2020;9(5):1444. doi: https://doi.org/10.3390/jcm9051444. PMID: 32413981.
5. Hydeman JA, Uwazurike OC, Adeyemi EI, et al. Survivorship needs of adolescent and young adult cancer survivors: a concept mapping analysis. J Cancer Surviv. 2019 Feb;13(1):34-42. doi: https://doi.org/10.1007/s11764-018-0725-5. PMID: 30604138.
6. Shapiro CL. Cancer Survivorship. N Engl J Med. 2018 Dec 20;379(25):2438-50. doi: https://doi.org/10.1056/NEJMra1712502. PMID: 30575480.
7. Lim PS, Tran S, Kroeze SGC, et al. Outcomes of adolescents and young adults treated for brain and skull base tumors with pencil beam scanning proton therapy. Pediatric Blood & Cancer. 2020;67(12):e28664. doi: https://doi.org/10.1002/pbc.28664.
8. Abrahao R, Li QW, Malogolowkin MH, et al. Chronic medical conditions and late effects following non-Hodgkin lymphoma in HIV-uninfected and HIV-infected adolescents and young adults: a population-based study. British Journal of Haematology. 2020 08;190(3):371-84. doi: https://dx.doi.org/10.1111/bjh.16539. PMID: 32080836.
9. Abrahão R, Huynh JC, Benjamin DJ, et al. Chronic medical conditions and late effects after acute myeloid leukaemia in adolescents and young adults: a population-based study. International Journal of Epidemiology. 2020;50(2):663-74. doi: https://doi.org/10.1093/ije/dyaa184.
10. Chao C, Xu L, Bhatia S, et al. Cardiovascular Disease Risk Profiles in Survivors of Adolescent and Young Adult (AYA) Cancer: The Kaiser Permanente AYA Cancer Survivors Study. J Clin Oncol. 2016 May 10;34(14):1626-33. doi: https://doi.org/10.1200/jco.2015.65.5845. PMID: 26951318.
11. Chao C, Bhatia S, Xu L, et al. Chronic Comorbidities Among Survivors of Adolescent and Young Adult Cancer. J Clin Oncol. 2020 Sep 20;38(27):3161-74. doi: https://doi.org/10.1200/jco.20.00722. PMID: 32673152.

12. Hamilton SN, Arshad O, Kwok J, et al. Documentation and incidence of late effects and screening recommendations for adolescent and young adult head and neck cancer survivors treated with radiotherapy. Supportive Care in Cancer. 2019 2019/07/01;27(7):2609-16. doi: https://doi.org/10.1007/s00520-018-4559-5.
13. Liuhto N, Gronroos MH, Malila N, et al. Diseases of renal function and bone metabolism after treatment for early onset cancer: A registry-based study. International Journal of Cancer. 2020 03 01;146(5):1324-32. doi: https://dx.doi.org/10.1002/ijc.32687. PMID: 31523804.
14. Rugbjerg K, Olsen JH. Long-term Risk of Hospitalization for Somatic Diseases in Survivors of Adolescent or Young Adult Cancer. JAMA Oncology. 2016 Feb;2(2):193-200. doi: https://dx.doi.org/10.1001/jamaoncol.2015.4393. PMID: 26584448.
15. Semrad TJ, Li Q, Goldfarb M, et al. Influence of Socioeconomic Status on Incident Medical Conditions in Two-Year Survivors of Adolescent or Young Adult Differentiated Thyroid Cancer. Journal of Adolescent & Young Adult Oncology. 2021 Jan 28;28:28. doi: https://dx.doi.org/10.1089/jayao.2020.0142. PMID: 33512275.
16. Bohn SH, Thorsen L, Kiserud CE, et al. Chronic fatigue and associated factors among long-term survivors of cancers in young adulthood. Acta Oncologica. 2019 May;58(5):753-62. doi: https://dx.doi.org/10.1080/0284186X.2018.1557344. PMID: 30696351.
17. Feldman DR, Ardeshir-Rouhani-Fard S, Monahan P, et al. Predicting Cardiovascular Disease Among Testicular Cancer Survivors After Modern Cisplatin-based Chemotherapy: Application of the Framingham Risk Score. Clinical Genitourinary Cancer. 2018 08;16(4):e761-e9. doi: https://dx.doi.org/10.1016/j.clgc.2018.01.011. PMID: 29534941.
18. Chao C, Bhatia S, Xu L, et al. Incidence, Risk Factors, and Mortality Associated With Second Malignant Neoplasms Among Survivors of Adolescent and Young Adult Cancer. JAMA Netw Open. 2019 Jun 5;2(6):e195536. doi: https://doi.org/10.1001/jamanetworkopen.2019.5536. PMID: 31173129.
19. Lee JS, DuBois SG, Coccia PF, et al. Increased risk of second malignant neoplasms in adolescents and young adults with cancer. Cancer. 2016 Jan 01;122(1):116-23. doi: https://dx.doi.org/10.1002/cncr.29685. PMID: 26441212.
20. Lo AC, Chen B, Samuel V, et al. Late effects in survivors treated for lymphoma as adolescents and young adults: a population-based analysis. J Cancer Surviv. 2021 Jan 16. doi: https://doi.org/10.1007/s11764-020-00976-7. PMID: 33453004.
21. Muffly L, Maguire FB, Li Q, et al. Late Effects in Survivors of Adolescent and Young Adult Acute Lymphoblastic Leukemia. JNCI Cancer Spectr. 2020 Aug;4(4):pkaa025. doi: https://doi.org/10.1093/jncics/pkaa025. PMID: 32704618.
22. Xie L, Lin C, Zhang H, et al. Second malignancy in young early-stage breast cancer patients with modern radiotherapy: A long-term population-based study (A STROBE-compliant study). Medicine. 2018 Apr;97(17):e0593. doi: https://dx.doi.org/10.1097/MD.0000000000010593. PMID: 29703057.
23. Armenian SH, Xu L, Cannavale KL, et al. Cause-specific mortality in survivors of adolescent and young adult cancer. Cancer. 2020 May 15;126(10):2305-16. doi: https://doi.org/10.1002/cncr.32775. PMID: 32129881.
24. Bhuller KS, Zhang Y, Li D, et al. Late mortality, secondary malignancy and hospitalisation in teenage and young adult survivors of Hodgkin lymphoma: report of the Childhood/Adolescent/Young Adult Cancer Survivors Research Program and the BC Cancer Agency Centre for Lymphoid Cancer. British Journal of Haematology. 2016 Mar;172(5):757-68. doi: https://dx.doi.org/10.1111/bjh.13903. PMID: 26727959.
25. Goldfarb M, Rosenberg AS, Li Q, et al. Impact of latency time on survival for adolescents and young adults with a second primary malignancy. Cancer. 2018 03 15;124(6):1260-8. doi: https://dx.doi.org/10.1002/cncr.31170. PMID: 29205296.

26. Suh E, Stratton KL, Leisenring WM, et al. Late mortality and chronic health conditions in long-term survivors of early-adolescent and young adult cancers: a retrospective cohort analysis from the Childhood Cancer Survivor Study. Lancet Oncology. 2020 03;21(3):421-35. doi: https://dx.doi.org/10.1016/S1470-2045(19)30800-9. PMID: 32066543.
27. Tzikas AK, Nemes S, Linderholm BK. A comparison between young and old patients with triple-negative breast cancer: biology, survival and metastatic patterns. Breast Cancer Research & Treatment. 2020 Aug;182(3):643-54. doi: https://dx.doi.org/10.1007/s10549-020-05727-x. PMID: 32524352.
28. Wettergren L, Kent EE, Mitchell SA, et al. Cancer negatively impacts on sexual function in adolescents and young adults: The AYA HOPE study. Psycho-Oncology. 2017 Oct;26(10):1632-9. doi: https://dx.doi.org/10.1002/pon.4181. PMID: 27240019.
29. Ahomaki R, Kero A, Koivisto M, et al. Purchases of antidepressants after cancer at a young age in Finland. International Journal of Cancer. 2019 03 15;144(6):1227-33. doi: https://dx.doi.org/10.1002/ijc.31942. PMID: 30357818.
30. Olsson M, Enskar K, Steineck G, et al. Self-Perceived Physical Attractiveness in Relation to Scars Among Adolescent and Young Adult Cancer Survivors: A Population-Based Study. Journal of Adolescent & Young Adult Oncology. 2018 06;7(3):358-66. doi: https://dx.doi.org/10.1089/jayao.2017.0089. PMID: 29373051.
31. Shay LA, Carpentier MY, Vernon SW. Prevalence and correlates of fear of recurrence among adolescent and young adult versus older adult post-treatment cancer survivors. Supportive Care in Cancer. 2016 11;24(11):4689-96. doi: https://dx.doi.org/10.1007/s00520-016-3317-9. PMID: 27387913.
32. Chemerinski A, Cameron K, Sammel M, et al. Relationship of menopausal symptoms and ovarian reserve in reproductive-aged cancer survivors. Journal of Cancer Survivorship. 2020 10;14(5):607-13. doi: https://dx.doi.org/10.1007/s11764-020-00857-z. PMID: 32323140.
33. Johnson L, Sammel MD, Schanne A, et al. Female cancer survivors exposed to alkylating-agent chemotherapy have unique reproductive hormone profiles. Fertility & Sterility. 2016 Dec;106(7):1793-9.e2. doi: https://dx.doi.org/10.1016/j.fertnstert.2016.08.041. PMID: 27666565.
34. Su HI, Kwan B, Whitcomb BW, et al. Modeling Variation in the Reproductive Lifespan of Female Adolescent and Young Adult Cancer Survivors Using AMH. Journal of Clinical Endocrinology & Metabolism. 2020 08 01;105(8):01. doi: https://dx.doi.org/10.1210/clinem/dgaa172. PMID: 32270202.
35. Abe A, Kuwahara A, Iwasa T, et al. A survey on fertility management in young women of reproductive age treated with chemotherapy. International Journal of Clinical Oncology. 2016 Dec;21(6):1183-90. PMID: 27402102.
36. Chin HB, Jacobson MH, Interrante JD, et al. Hypothyroidism after cancer and the ability to meet reproductive goals among a cohort of young adult female cancer survivors. Fertility & Sterility. 2016 Jan;105(1):202-7.e1-2. doi: https://dx.doi.org/10.1016/j.fertnstert.2015.09.031. PMID: 26474733.
37. Benedict C, Thom B, Friedman DN, et al. Fertility information needs and concerns post-treatment contribute to lowered quality of life among young adult female cancer survivors. Supportive Care in Cancer. 2018 Jul;26(7):2209-15. doi: https://dx.doi.org/10.1007/s00520-017-4006-z. PMID: 29387996.
38. Hartnett KP, Mertens AC, Kramer MR, et al. Pregnancy after cancer: Does timing of conception affect infant health? Cancer. 2018 11 15;124(22):4401-7. doi: https://dx.doi.org/10.1002/cncr.31732. PMID: 30403424.
39. Jacobson MH, Mertens AC, Spencer JB, et al. Menses resumption after cancer treatment-induced amenorrhea occurs early or not at all. Fertility & Sterility. 2016 Mar;105(3):765-72.e4. doi: https://dx.doi.org/10.1016/j.fertnstert.2015.11.020. PMID: 26658130.

40. Shandley LM, Spencer JB, Fothergill A, et al. Impact of tamoxifen therapy on fertility in breast cancer survivors. Fertility & Sterility. 2017 01;107(1):243-52.e5. doi: https://dx.doi.org/10.1016/j.fertnstert.2016.10.020. PMID: 27887709.
41. Shandley LM, Fothergill A, Spencer JB, et al. Impact of cancer treatment on risk of infertility and diminished ovarian reserve in women with polycystic ovary syndrome. Fertility & Sterility. 2018 03;109(3):516-25.e1. doi: https://dx.doi.org/10.1016/j.fertnstert.2017.11.016. PMID: 29428311.
42. Isaksson S, Bogefors K, Akesson K, et al. Risk of low bone mineral density in testicular germ cell cancer survivors: association with hypogonadism and treatment modality. Andrology. 2017 Sep;5(5):898-904. doi: https://dx.doi.org/10.1111/andr.12383. PMID: 28591464.
43. Ha J, Park SS, Park S, et al. Effects of Hormone Replacement Therapy on Bone Mass After Allogeneic Hematopoietic Stem Cell Transplantation. Journal of Clinical Endocrinology & Metabolism. 2020 09 01;105(9):01. doi: https://dx.doi.org/10.1210/clinem/dgaa406. PMID: 32594134.

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Appendix A: Methods

We assessed the nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

In response to the submitted nomination, we conducted a search for existing systematic reviews. We searched for high-quality, completed or in-process evidence reviews published in the last three years, June 1, 2018 to June 1, 2021 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
    - AHRQ Evidence Reports https://www.ahrq.gov/research/findings/evidence-based-reports/index.html
    - EHC Program https://effectivehealthcare.ahrq.gov/
    - US Preventive Services Task Force https://www.uspreventiveservicestaskforce.org/
    - AHRQ Technology Assessment Program https://www.ahrq.gov/research/findings/ta/index.html
- US Department of Veterans Affairs Products publications
    - Evidence Synthesis Program https://www.hsrd.research.va.gov/publications/esp/
    - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program https://www.healthquality.va.gov/
- Cochrane Systematic Reviews https://www.cochranelibrary.com/
- PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
- PubMed https://www.ncbi.nlm.nih.gov/pubmed/

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

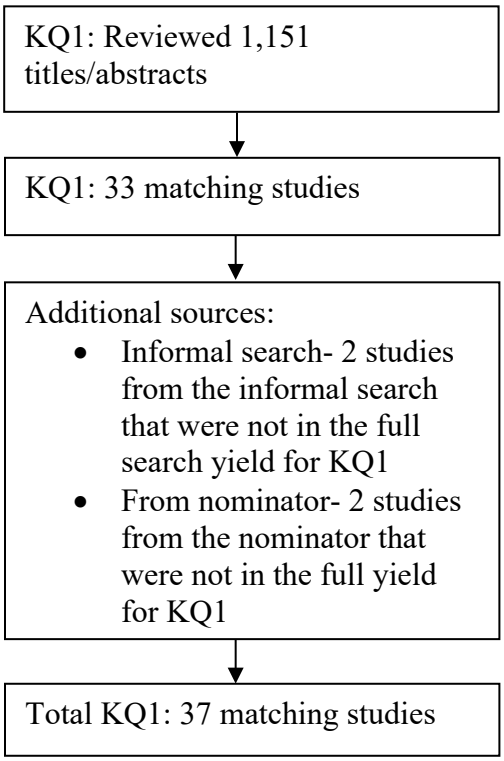
We conducted a literature search in PubMed/Ovid MEDLINE limited to the last five years, June 1, 2016 – June 1, 2021.

Limited review of the literature search yield for topic development phase

In the process of the initial topic development process, we identified 1,151 primary studies, but reviewed a sample of 200 for KQ1 due to the large yield. Because of the limited number of studies identified from that review of 200 studies, we identified additional relevant studies

through an informal search in PubMed using keywords (cancer, late effects, young adults). We examined the first 100 studies, which corresponded with studies published from August 2020 to the present. In addition, we included suggestions from the nominator. For KQ2, we did not find any studies from a review of the entire formal search yield or from the additional sources (the informal search or the studies provided by the nominator).

Detailed review of the literature search yield for development of the expanded topic brief tables
For the subsequent development of the included evidence tables (Tables 2a-f), we reviewed all 1,151 studies from the search for KQ1. In addition to the studies found in the formal search, Tables 2a-f include two additional studies from the described informal search and two from the nominators' suggestions.



Search strategy
1 Cancer Survivors/ or ((cancer* adj3 surviv*) or survivorship).ti,ab,kf. (74119)
2 Young Adult/ or (CAYA or YA or ((early or young) adj (adult* or men or people or women))).ti,kf. (955056)
3 exp Immunotherapy/ or exp Organ Transplantation/ or exp Radiotherapy/ or exp Surgical Procedures, Operative/ or (chemotherapy or chemoradiotherapy).hw. or (chemotherap* or chemo-therap* or immunotherap* or immuno-therap* or radiation or surgical or surger* or transplant*).ti,ab,kf. or (dt or rt or su or th).fs. (8605084)

4 ((adverse adj (effect* or event*)) or harm* or (late adj3 effect*)).ti,ab,kf. or (ae or co or de or in or mo or po or re).fs. (7435889)
5 and/1-4 (2341)
6 5 not ((exp Animals/ not Humans/) or (letter or comment or case report or editorial or news).pt.) (2323)
7 limit 6 to english language (2285)
8 (meta-analysis or systematic review).pt. or (metaanal* or meta-anal* or ((evidence or systematic) adj3 (review or synthesis))).ti,kf. (298372)
9 and/7-8 (39)
10 limit 9 to yr="2018 -Current" (16) KQ1 SYSTEMATIC REVIEWS/META-ANALYSES
11 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ or ((control and (group* or study)) or (time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (10127694)
12 and/7,11 (2155)
13 limit 12 to yr="2016 -Current" (1167) KQ1 – NONRANDOMIZED STUDIES
14 Cancer Survivors/ or ((cancer* adj3 surviv*) or survivorship).ti,ab,kf. (74119)
15 Young Adult/ or (CAYA or YA or ((early or young) adj (adult* or men or people or women))).ti,kf. (955056)
16 Mass screening/ or (screen* or surveill*).ti,kf. (313912)
17 and/14-16 (202)
18 17 not ((exp Animals/ not Humans/) or (letter or comment or case report or editorial or news).pt.) (198)
19 limit 18 to english language (198)
20 (meta-analysis or systematic review).pt. or (metaanal* or meta-anal* or ((evidence or systematic) adj3 (review or synthesis))).ti,kf. (298372)
21 and/19-20 (5)
22 limit 21 to yr="2018 -Current" (4) KQ2 SYSTEMATIC REVIEWS/META-ANALYSES
23 exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/ or ((control and (group* or study)) or (time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp. (10127694)
24 and/19,23 (180)
25 limit 24 to yr="2016 -Current" (109) KQ2 – NONRANDOMIZED STUDIES

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the United States?	Yes.
1b. Is the nomination a request for an evidence report?	Yes.
1c. Is the focus on effectiveness or comparative effectiveness?	No.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	About 5% (89,000) of cancer diagnoses in the United States each year are in young people ages 15 to 39.[1]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the United States population or for a vulnerable population	Some aspects of cancer in the young adult age group may be unique and there are not currently guidelines specifically for survivors for this age group.
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes.
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	From 2008-2010, the annual cost for cancer survivors ages 18 to 64 was $16,213 per survivor.[2] Little evaluation of the financial impact on young adults and their families has been conducted, despite their particular vulnerability to the financial burden of cancer care.[3]
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	No scoping reviews to address the KQs were identified.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. While guidelines for cancer survivors diagnosed as children or adults exist, guidelines for cancer survivors diagnosed as young adults do not. Due to specific needs of young adult survivors, guidelines for this group are needed.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes. In the absence of guidelines specifically created for young adults, care providers often have to extrapolate from guidelines for children and adults to make decisions for this population.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	KQ1: For the included Tables 2a-f, we reviewed the entire search yield of 1,151 studies and found 33 studies. Additionally, we included in the tables 2 studies provided by the nominator and 2 studies identified in an informal search, for a total of 37 studies. These 37 studies had varied cancer types, treatment types, and outcome measures.

	Thus, this collection of studies was not appropriate for a SR, but lent itself to display in the form of Tables 2a-f. KQ2: No primary studies found.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; ASCO=American Society of Clinical Oncology; KQ=key question; SR=systematic review